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(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of the following applications: (1) application Ser. No. 09/079,124, filed May 14, 1998, which is a continuation-in-part of provisional application Ser. No. 60/077,521, filed March 11, 1998; and (2) provisional application Ser. No. 60/077,521, filed March 11, 1998; all of which are incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cb98_4 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone cb98_4 deposited under accession number ATCC 98689;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:2;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ;

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h); and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h) and that has a length that is at least 25% of the length of SEQ ID NO:1.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857; the nucleotide sequence of the full-length

protein coding sequence of clone cb98_4 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone cb98_4 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:2, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 295 to amino acid 304 of SEQ ID NO:2.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:1, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:1; and

(ab) the nucleotide sequence of the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:1, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:1; and

(bb) the nucleotide sequence of the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:1 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:1 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:1. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) a fragment of the amino acid sequence of SEQ ID NO:2, the fragment comprising eight contiguous amino acids of SEQ ID NO:2; and

(c) the amino acid sequence encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:2, or a protein comprising a fragment of the amino acid sequence of SEQ

ID NO:2 having biological activity, the fragment comprising the amino acid sequence from amino acid 295 to amino acid 304 of SEQ ID NO:2.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du515_21 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone du515_21 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:4;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ;

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i); and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i) and that has a length that is at least 25% of the length of SEQ ID NO:3.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718; the nucleotide sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718; the nucleotide sequence of the full-length protein coding sequence of clone du515_21 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone du515_21 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:4, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 86 to amino acid 95 of SEQ ID NO:4.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:3, but excluding the poly(A) tail at the 3' end of SEQ ID NO:3; and

(ab) the nucleotide sequence of the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:3, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:3; and

(bb) the nucleotide sequence of the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:3 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:3 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:3. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) a fragment of the amino acid sequence of SEQ ID NO:4, the fragment comprising eight contiguous amino acids of SEQ ID NO:4; and

(c) the amino acid sequence encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:4, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity, the fragment comprising the amino acid sequence from amino acid 86 to amino acid 95 of SEQ ID NO:4.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 411 to nucleotide 638;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:6;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ;

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i); and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i) and that has a length that is at least 25% of the length of SEQ ID NO:5.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638; the nucleotide sequence of SEQ ID NO:5 from nucleotide 411 to nucleotide 638; the nucleotide sequence of the full-length protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:6, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 44 to amino acid 53 of SEQ ID NO:6.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:5, but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(ab) the nucleotide sequence of the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:5, but excluding the poly(A) tail at the 3' end of SEQ ID NO:5; and

(bb) the nucleotide sequence of the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:5 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:5 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:5. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:5 from nucleotide 411 to nucleotide 638, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:5 from

nucleotide 411 to nucleotide 638, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:5 from nucleotide 411 to nucleotide 638.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) a fragment of the amino acid sequence of SEQ ID NO:6, the fragment comprising eight contiguous amino acids of SEQ ID NO:6; and

(c) the amino acid sequence encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:6, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity, the fragment comprising the amino acid sequence from amino acid 44 to amino acid 53 of SEQ ID NO:6.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(g) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755;

(h) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:8;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ;

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j); and

(n) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(j) and that has a length that is at least 25% of the length of SEQ ID NO:7.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959; the nucleotide sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959; the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385; the nucleotide sequence of the full-length protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755; or the nucleotide sequence of a mature protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 268. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:8, or a

polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 144 to amino acid 153 of SEQ ID NO:8.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:7, but excluding the poly(A) tail at the 3' end of SEQ ID NO:7; and

(ab) the nucleotide sequence of the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:7, but excluding the poly(A) tail at the 3' end of SEQ ID NO:7; and

(bb) the nucleotide sequence of the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7, and extending

contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:7 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:7 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:7. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 268;

(c) a fragment of the amino acid sequence of SEQ ID NO:8, the fragment comprising eight contiguous amino acids of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 268. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid

sequence of SEQ ID NO:8 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:8, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity, the fragment comprising the amino acid sequence from amino acid 144 to amino acid 153 of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:10;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ;

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i); and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i) and that has a length that is at least 25% of the length of SEQ ID NO:9.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895; the nucleotide sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895; the nucleotide sequence of the full-length protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:10, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 88 to amino acid 97 of SEQ ID NO:10.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:9, but excluding the poly(A) tail at the 3' end of SEQ ID NO:9; and

(ab) the nucleotide sequence of the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:9, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:9; and

(bb) the nucleotide sequence of the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:9 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:9 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:9. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) a fragment of the amino acid sequence of SEQ ID NO:10, the fragment comprising eight contiguous amino acids of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:10, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity, the fragment comprising the amino acid sequence from amino acid 88 to amino acid 97 of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 305 to nucleotide 928;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:12;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ;

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i); and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i) and that has a length that is at least 25% of the length of SEQ ID NO:11.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 305 to nucleotide 928; the nucleotide sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928; the nucleotide sequence of the full-length protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:12, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 99 to amino acid 108 of SEQ ID NO:12.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(ab) the nucleotide sequence of the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:11, but excluding the poly(A) tail at the 3' end of SEQ ID NO:11; and

(bb) the nucleotide sequence of the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:11 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:11 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:11. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 305 to nucleotide 928, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from nucleotide 305 to nucleotide 928, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide

305 to nucleotide 928. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) a fragment of the amino acid sequence of SEQ ID NO:12, the fragment comprising eight contiguous amino acids of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:12, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity, the fragment comprising the amino acid sequence from amino acid 99 to amino acid 108 of SEQ ID NO:12.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pp85_1 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone pp85_1 deposited under accession number ATCC 98689;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:14;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ;

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h); and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h) and that has a length that is at least 25% of the length of SEQ ID NO:13.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792; the nucleotide sequence of the full-length protein coding sequence of clone pp85_1 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone pp85_1 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:14, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 20 to amino acid 29 of SEQ ID NO:14.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:13, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:13; and

(ab) the nucleotide sequence of the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:13, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:13; and

(bb) the nucleotide sequence of the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:13 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:13 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:13. Also preferably the

polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) a fragment of the amino acid sequence of SEQ ID NO:14, the fragment comprising eight contiguous amino acids of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:14, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity, the fragment comprising the amino acid sequence from amino acid 20 to amino acid 29 of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pp325_9 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone pp325_9 deposited under accession number ATCC 98689;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:16;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ;

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h); and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h) and that has a length that is at least 25% of the length of SEQ ID NO:15.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931; the nucleotide sequence of the full-length protein coding sequence of clone pp325_9 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone pp325_9 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:16, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 43 to amino acid 52 of SEQ ID NO:16.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:15, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:15; and

(ab) the nucleotide sequence of the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:15, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:15; and

(bb) the nucleotide sequence of the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:15 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:15 , but excluding the poly(A) tail at the 3′ end of SEQ ID NO:15. Also preferably the

polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) a fragment of the amino acid sequence of SEQ ID NO:16, the fragment comprising eight contiguous amino acids of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:16, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity, the fragment comprising the amino acid sequence from amino acid 43 to amino acid 52 of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone qb401_6 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

(e) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone qb401_6 deposited under accession number ATCC 98689;

(f) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:18;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ;

(k) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h); and

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(h) and that has a length that is at least 25% of the length of SEQ ID NO:17.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443; the nucleotide sequence of the full-length protein coding sequence of clone qb401_6 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone qb401_6 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:18, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 57 to amino acid 66 of SEQ ID NO:18.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(ab) the nucleotide sequence of the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:17, but excluding the poly(A) tail at the 3' end of SEQ ID NO:17; and

(bb) the nucleotide sequence of the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ ID NO:17 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:17 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:17. Also preferably the

polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) a fragment of the amino acid sequence of SEQ ID NO:18, the fragment comprising eight contiguous amino acids of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:18, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity, the fragment comprising the amino acid sequence from amino acid 57 to amino acid 66 of SEQ ID NO:18.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of a mature protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding a mature protein encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising eight contiguous amino acids of SEQ ID NO:20;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ;

(l) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i); and

(m) a polynucleotide that hybridizes under stringent conditions to any one of the polynucleotides specified in (a)-(i) and that has a length that is at least 25% of the length of SEQ ID NO:19.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381; the nucleotide sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381; the nucleotide sequence of the full-length protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689; or the nucleotide sequence of a mature protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689. In other preferred embodiments, the polynucleotide encodes the full-length or a mature protein encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689. In further preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:20, or a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having

biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

Further embodiments of the invention provide isolated polynucleotides produced according to a process selected from the group consisting of:

(a) a process comprising the steps of:

(i) preparing one or more polynucleotide probes that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(aa) SEQ ID NO:19, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:19; and

(ab) the nucleotide sequence of the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(ii) hybridizing said probe(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C; and

(iii) isolating the DNA polynucleotides detected with the probe(s);

and

(b) a process comprising the steps of:

(i) preparing one or more polynucleotide primers that hybridize in 6X SSC at 65 degrees C to a nucleotide sequence selected from the group consisting of:

(ba) SEQ ID NO:19, but excluding the poly(A) tail at the 3′ end of SEQ ID NO:19; and

(bb) the nucleotide sequence of the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(ii) hybridizing said primer(s) to human genomic DNA in conditions at least as stringent as 4X SSC at 50 degrees C;

(iii) amplifying human DNA sequences; and

(iv) isolating the polynucleotide products of step (b)(iii).

Preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19, and extending contiguously from a nucleotide sequence corresponding to the 5' end of SEQ

ID NO:19 to a nucleotide sequence corresponding to the 3' end of SEQ ID NO:19 , but excluding the poly(A) tail at the 3' end of SEQ ID NO:19. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381. Also preferably the polynucleotide isolated according to the above process comprises a nucleotide sequence corresponding to the cDNA sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381, and extending contiguously from a nucleotide sequence corresponding to the 5' end of said sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381, to a nucleotide sequence corresponding to the 3' end of said sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) a fragment of the amino acid sequence of SEQ ID NO:20, the fragment comprising eight contiguous amino acids of SEQ ID NO:20; and

(c) the amino acid sequence encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20. In further preferred embodiments, the present invention provides a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment preferably comprising eight (more preferably twenty, most preferably thirty) contiguous amino acids of SEQ ID NO:20, or a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity, the fragment comprising the amino acid sequence from amino acid 33 to amino acid 42 of SEQ ID NO:20.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or

modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature forms) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal

sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "cb98_4"

A polynucleotide of the present invention has been identified as clone "cb98_4". cb98_4 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. cb98_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "cb98_4 protein").

The nucleotide sequence of cb98_4 as presently determined is reported in SEQ ID NO:1, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the cb98_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone cb98_4 should be approximately 2200 bp.

The nucleotide sequence disclosed herein for cb98_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. cb98_4 demonstrated at least some similarity with sequences identified as AA178965 (zp39f09.s1 Stratagene muscle 937209 Homo sapiens cDNA clone 611849 3'), AA290723 (zs44c07.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:700332 5'), AA573499 (nk99f01.s1 NCI_CGAP_Co3 Homo sapiens cDNA clone IMAGE:1028953), R23530 (yg29g12.r1 Homo sapiens cDNA clone 34025 5'), and T09374 (EST07267 Homo sapiens cDNA clone HIBBT41 5' end). The predicted amino acid sequence disclosed herein for cb98_4 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted cb98_4 protein demonstrated at least some similarity to sequences identified as M21665 (beta-myosin heavy chain [Homo sapiens]), U93871 (RaP2 interacting protein 8 [Homo sapiens]), and X78998 (endosomal protein [Homo sapiens]). Based upon sequence similarity, cb98_4 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts two potential transmembrane

domains within the cb98_4 protein sequence, centered around amino acids 28 and 140 of SEQ ID NO:2; amino acids 15 to 27 are also a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 28.

Clone "du515_21"

A polynucleotide of the present invention has been identified as clone "du515_21". du515_21 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. du515_21 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "du515_21 protein").

The nucleotide sequence of du515_21 as presently determined is reported in SEQ ID NO:3, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the du515_21 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 51 to 63 of SEQ ID NO:4 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 64. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the du515_21 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone du515_21 should be approximately 1300 bp.

The nucleotide sequence disclosed herein for du515_21 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. du515_21 demonstrated at least some similarity with sequences identified as AA124621 (mp72d01.r1 Soares 2NbMT Mus musculus cDNA clone 574753 5'), AA602397 (no30d06.s1 NCI_CGAP_Pr22 Homo sapiens cDNA clone IMAGE:1102187), M78422 (EST00570 Homo sapiens cDNA clone HFBCB84), Q59591 (Human brain Expressed Sequence Tag EST00580), T04884 (EST02772 Homo sapiens cDNA clone HFBCB84), and W31206 (zb95a05.s1 Soares parathyroid tumor NbHPA Homo sapiens cDNA clone 320528 3'). The predicted amino acid sequence disclosed herein for du515_21 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted du515_21 protein demonstrated at least some

similarity to sequences identified as L31611 (NMDA receptor subunit NR2D [Rattus norvegicus]) and Z15045 (glycine-rich_protein_(aa1-291) [Brassica napus]). Based upon sequence similarity, du515_21 proteins and each similar protein or peptide may share at least some activity.

Clone "gn82_6"

A polynucleotide of the present invention has been identified as clone "gn82_6". gn82_6 was isolated from a human adult blood (peripheral blood mononuclear cells treated with granulocyte-colony stimulating factor *in vivo*) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. gn82_6 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "gn82_6 protein").

The nucleotide sequence of gn82_6 as presently determined is reported in SEQ ID NO:5, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the gn82_6 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 11 to 23 of SEQ ID NO:6 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the gn82_6 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone gn82_6 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for gn82_6 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. gn82_6 demonstrated at least some similarity with sequences identified as AA102622 (zn43f05.s1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 550209 3'), AA145264 (mr12h02.r1 Soares mouse 3NbMS Mus musculus cDNA clone 597267 5'), AA418655 (zv93g07.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 767388 5'), AA527345 (ng40a02.s1 NCI_CGAP_Co3 Homo sapiens cDNA clone IMAGE:937226), R98908 (yr31c08.r1 Homo sapiens cDNA clone 206894 5'), and W72745 (zd71f04.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346111 3' similar to WP:T26A5.7

CE00786 TRX). The predicted amino acid sequence disclosed herein for gn82_6 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted gn82_6 protein demonstrated at least some similarity to sequences identified as U00043 (similar to D. melanogaster trithorax protein [Caenorhabditis elegans]). Based upon sequence similarity, gn82_6 proteins and each similar protein or peptide may share at least some activity.

gn82_6 protein was expressed in a COS cell expression system, and an expressed protein band of approximately 18 kDa was detected in conditioned medium fractions using SDS polyacrylamide gel electrophoresis.

Clone "ij1442_1"

A polynucleotide of the present invention has been identified as clone "ij1442_1". ij1442_1 was isolated from a human adult blood (peripheral blood mononuclear cells treated with granulocyte-colony stimulating factor *in vivo*) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. ij1442_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "ij1442_1 protein").

The nucleotide sequence of ij1442_1 as presently determined is reported in SEQ ID NO:7, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the ij1442_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 51 to 63 of SEQ ID NO:8 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 64. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the ij1442_1 protein. The ATG sequence at positions 183-185 of SEQ ID NO:7 is another possible translation initiation codon.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone ij1442_1 should be approximately 1100 bp.

The nucleotide sequence disclosed herein for ij1442_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. ij1442_1 demonstrated at least some similarity with sequences

identified as AA150849 (zl44b01.r1 Soares pregnant uterus NbHPU Homo sapiens cDNA clone 504745 5'), AF012536 (Homo sapiens decoy receptor 1 (DcR1) mRNA, complete cds), AF016267 (Homo sapiens TRAIL receptor 3 mRNA, complete cds). The predicted amino acid sequence disclosed herein for ij1442_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted ij1442_1 protein demonstrated at least some similarity to sequences identified as AF012536 (decoy receptor 1 [Homo sapiens]), AF012629 (antagonist decoy receptor for TRAIL/Apo-2L [Homo sapiens]), AF014794 (TNF related TRAIL receptor [Homo sapiens]), AF016267 (TRAIL receptor 3 [Homo sapiens]), AF020502 (cytotoxic TRAIL receptor-3 [Homo sapiens]), AF033854 (lymphocyte inhibitor of TRAIL [Homo sapiens]), and U90875 (cytotoxic ligand TRAIL receptor [Homo sapiens]). Based upon sequence similarity, ij1442_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts an additional potential trans-membrane domain within the ij1442_1 protein sequence centered around amino acid 289 of SEQ ID NO:8.

ij1442_1 protein was expressed in a COS cell expression system, and an expressed protein band of approximately 23 kDa was detected in conditioned medium and membrane fractions using SDS polyacrylamide gel electrophoresis.

Clone "pe213_1"

A polynucleotide of the present invention has been identified as clone "pe213_1". pe213_1 was isolated from a human adult blood (chronic myelogenous leukemia K562) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. pe213_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "pe213_1 protein").

The nucleotide sequence of pe213_1 as presently determined is reported in SEQ ID NO:9, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the pe213_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10. Amino acids 145 to 157 of SEQ ID NO:10 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 158. Due to the

hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the pe213_1 protein.

Another potential pe213_1 reading frame and predicted amino acid sequence is encoded by basepairs 645 to 947 of SEQ ID NO:9 and is reported in SEQ ID NO:31. Amino acids 38 to 50 of SEQ ID NO:31 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 51. Due to the hydrophobic nature of this predicted leader/signal sequence, it is likely to act as a transmembrane domain should it not be separated from the remainder of the protein of SEQ ID NO:31. The TopPredII computer program predicts an additional potential transmembrane domain within the SEQ ID NO:31 amino acid sequence centered around amino acid 11 of SEQ ID NO:31.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone pe213_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for pe213_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. pe213_1 demonstrated at least some similarity with sequences identified as AA374638 (EST87065 HSC172 cells I Homo sapiens cDNA 5' end), AA421991 (zv26a08.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 754742 5'), AA424905 (zw03f01.s1 Soares NhHMPu S1 Homo sapiens cDNA clone 768217 3'), Q77233 (Human genome fragment), and R75637 (yi59d05.s1 Homo sapiens cDNA clone 143529 3'). Based upon sequence similarity, pe213_1 proteins and each similar protein or peptide may share at least some activity.

pe213_1 protein was expressed in a COS cell expression system, and an expressed protein band of approximately 10 kDa was detected in membrane fractions using SDS polyacrylamide gel electrophoresis.

Clone "pe318_4"

A polynucleotide of the present invention has been identified as clone "pe318_4". pe318_4 was isolated from a human adult blood (chronic myelogenous leukemia K562) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded

protein. pe318_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "pe318_4 protein").

The nucleotide sequence of pe318_4 as presently determined is reported in SEQ ID NO:11, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the pe318_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 100 to 112 of SEQ ID NO:12 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 113. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the pe318_4 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone pe318_4 should be approximately 1300 bp.

The nucleotide sequence disclosed herein for pe318_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. pe318_4 demonstrated at least some similarity with sequences identified as AA466632 (ve12h12.r1 Soares mouse NbMH Mus musculus cDNA clone 817991 5'), AA583057 (nn80h04.s1 NCI_CGAP_Co9 Homo sapiens cDNA clone IMAGE:1090231), T25941 (Human gene signature HUMGS08174), and W02860 (za05c08.r1 Soares melanocyte 2NbHM Homo sapiens cDNA clone 291662 5'). The predicted amino acid sequence disclosed herein for pe318_4 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted pe318_4 protein demonstrated at least some similarity to sequences identified as Z79597 (C33A11.2 [Caenorhabditis elegans]). Based upon sequence similarity, pe318_4 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the pe318_4 protein sequence, centered around amino acids 40, 70, 110, and 160 of SEQ ID NO:12, respectively; amino acids 37 to 49 are also a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 50.

Clone "pp85_1"

A polynucleotide of the present invention has been identified as clone "pp85_1". pp85_1 was isolated from a human adult blood (lymphoblastic leukemia MOLT-4) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S.

Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. pp85_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "pp85_1 protein").

The nucleotide sequence of pp85_1 as presently determined is reported in SEQ ID NO:13, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the pp85_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Another potential pp85_1 reading frame and predicted amino acid sequence encoded by basepairs 121 to 384 of SEQ ID NO:13 is reported in SEQ ID NO:32.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone pp85_1 should be approximately 1200 bp.

The nucleotide sequence disclosed herein for pp85_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database. The TopPredII computer program predicts a potential transmembrane domain within the pp85_1 protein sequence centered around amino acid 26 of SEQ ID NO:14; amino acids 13 to 25 of SEQ ID NO:14 are also a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26. The nucleotide sequence of pp85_1 indicates that it may contain an Alu repetitive element.

Clone "pp325_9"

A polynucleotide of the present invention has been identified as clone "pp325_9". pp325_9 was isolated from a human adult blood (lymphoblastic leukemia MOLT-4) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. pp325_9 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "pp325_9 protein").

The nucleotide sequence of pp325_9 as presently determined is reported in SEQ ID NO:15, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the pp325_9 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone pp325_9 should be approximately 2200 bp.

The nucleotide sequence disclosed herein for pp325_9 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. pp325_9 demonstrated at least some similarity with sequences identified as R34384 (yh85h08.s1 Homo sapiens cDNA clone 136575 3' similar to contains Alu repetitive element). Based upon sequence similarity, pp325_9 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of pp325_9 indicates that it may contain an Alu repetitive element.

Clone "qb401_6"

A polynucleotide of the present invention has been identified as clone "qb401_6". qb401_6 was isolated from a human adult bladder (carcinoma 5637) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. qb401_6 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "qb401_6 protein").

The nucleotide sequence of qb401_6 as presently determined is reported in SEQ ID NO:17, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the qb401_6 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Another potential qb401_6 reading frame and predicted amino acid sequence encoded by basepairs 364 to 507 of SEQ ID NO:17 is reported in SEQ ID NO:33. Amino acids 6 to 18 of SEQ ID NO:33 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 19. Due to the hydrophobic nature of this predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the protein of SEQ ID NO:33.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone qb401_6 should be approximately 2200 bp.

The nucleotide sequence disclosed herein for qb401_6 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. No hits were found in the database. The TopPredII computer

program predicts two potential trans-membrane domains within the qb401_6 protein sequence of SEQ ID NO:18.

Clone "qc671_1"

A polynucleotide of the present invention has been identified as clone "qc671_1". qc671_1 was isolated from a human adult neural tissue (neuroepithelioma HTB-10 cell line) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. qc671_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "qc671_1 protein").

The nucleotide sequence of qc671_1 as presently determined is reported in SEQ ID NO:19, and includes a poly(A) tail. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the qc671_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20. Amino acids 13 to 25 of SEQ ID NO:20 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26. Due to the hydrophobic nature of the predicted leader/signal sequence, it is likely to act as a transmembrane domain should the predicted leader/signal sequence not be separated from the remainder of the qc671_1 protein.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone qc671_1 should be approximately 1100 bp.

The nucleotide sequence disclosed herein for qc671_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. qc671_1 demonstrated at least some similarity with sequences identified as AA699680 (zi78c08.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 446894 3'). Based upon sequence similarity, qc671_1 proteins and each similar protein or peptide may share at least some activity.

qc671_1 protein was expressed in a COS cell expression system, and an expressed protein band of approximately 11 kDa was detected in conditioned medium and membrane fractions using SDS polyacrylamide gel electrophoresis.

Deposit of Clones

Clones cb98_4, du515_21, gn82_6, ij1442_3, pe213_1, pe318_4, pp85_1, pp325_9, qb401_6, and qc671_1 were deposited on March 11, 1998 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and were given the accession number ATCC 98689, from which each clone comprising a particular polynucleotide is obtainable. Clone ij1442_1, an isolate related to clone ij1442_3, was deposited on May 14, 1998 with the American Type Culture Collection (10801 University Boulevard, Manassas, Virginia 20110-2209 U.S.A.) as an original deposit under the Budapest Treaty and was given the accession number ATCC 98755, from which the ij1442_1 clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b), and the term of the deposit will comply with 37 C.F.R. § 1.806.

Each clone has been transfected into separate bacterial cells (*E. coli*) in these composite deposits. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Figures 1A and 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* **9**: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of an

oligonucleotide probe that was used to isolate or to sequence each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
cb98_4	SEQ ID NO:21
du515_21	SEQ ID NO:22
gn82_6	SEQ ID NO:23
ij1442_1	SEQ ID NO:24
pe213_1	SEQ ID NO:25
pe318_4	SEQ ID NO:26
pp85_1	SEQ ID NO:27
pp325_9	SEQ ID NO:28
qb401_6	SEQ ID NO:29
qc671_1	SEQ ID NO:30

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as, for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with γ-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to

the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can

then be performed at an Internet site provided by the National Center for Biotechnology Information having the address http://www.ncbi.nlm.nih.gov/UniGene/, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* **15(7)**: 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* **62(1)**: 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* **58**: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* **14(9)**: 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* **90(16)**: 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* **91(2)**: 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* **336**: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms, part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information. For example, the TopPredII computer program can be used to predict the location of transmembrane domains in an amino acid sequence, domains which are described by the location of the center of the transmsmbrane domain, with at least ten transmembrane amino acids on each side of the reported central residue(s).

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* **266**: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* **215**: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* **3**: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, *Proc. Natl. Acad. Sci. USA* **90**: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from ftp://blast.wustl.edu/blast/executables. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is

provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian

species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes, Gorilla gorilla, Pongo pygmaeus, Hylobates concolor, Macaca mulatta, Papio papio, Papio hamadryas, Cercopithecus aethiops, Cebus capucinus, Aotus trivirgatus, Sanguinus oedipus, Microcebus murinus, Mus musculus, Rattus norvegicus, Cricetulus griseus, Felis catus, Mustela vison, Canis familiaris, Oryctolagus cuniculus, Bos taurus, Ovis aries, Sus scrofa,* and *Equus caballus,* for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682-690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* **13(10)**: 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art

given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, those described in Gyuris *et al.*, 1993, *Cell* **75**: 791-803 and in Rossi *et al.*, 1997, *Proc. Natl. Acad. Sci. USA* **94**: 8405-8410, all of which are incorporated by reference herein) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may

induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991;

Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease.

Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term

tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune

response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2

microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek,

D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid

cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and

Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and

in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation

of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al.

APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved

extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via antibody-dependent cell-mediated cytotoxicity (ADCC)). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s);

effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical

compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present

invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in

R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other

ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of

a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 58 to nucleotide 1857;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone cb98_4 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(f) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2, the fragment comprising eight contiguous amino acids of SEQ ID NO:2;

(g) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f); and

(h) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f), and that has a length that is at least 25% of the length of SEQ ID NO:1.

2. The polynucleotide of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with the polynucleotide of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by the polynucleotide of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. An isolated polynucleotide encoding the protein of claim 6.

8. The polynucleotide of claim 7, wherein the polynucleotide comprises the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689.

9. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) a fragment of the amino acid sequence of SEQ ID NO:2, the fragment comprising eight contiguous amino acids of SEQ ID NO:2; and

(c) the amino acid sequence encoded by the cDNA insert of clone cb98_4 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

10. The protein of claim 9, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

11. A composition comprising the protein of claim 9 and a pharmaceutically acceptable carrier.

12. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 170 to nucleotide 718;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 359 to nucleotide 718;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone du515_21 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone du515_21 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4, the fragment comprising eight contiguous amino acids of SEQ ID NO:4;

(j) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i); and

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i), and that has a length that is at least 25% of the length of SEQ ID NO:3.

13. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) a fragment of the amino acid sequence of SEQ ID NO:4, the fragment comprising eight contiguous amino acids of SEQ ID NO:4; and

(c) the amino acid sequence encoded by the cDNA insert of clone du515_21 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

14. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 342 to nucleotide 638;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 411 to nucleotide 638;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone gn82_6 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6, the fragment comprising eight contiguous amino acids of SEQ ID NO:6;

(j) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i); and

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i), and that has a length that is at least 25% of the length of SEQ ID NO:5.

15. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) a fragment of the amino acid sequence of SEQ ID NO:6, the fragment comprising eight contiguous amino acids of SEQ ID NO:6; and

(c) the amino acid sequence encoded by the cDNA insert of clone gn82_6 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

16. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 63 to nucleotide 959;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 252 to nucleotide 959;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 1 to nucleotide 385;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone ij1442_1 deposited under accession number ATCC 98755;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8, the fragment comprising eight contiguous amino acids of SEQ ID NO:8;

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(j); and

(l) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50%

formamide, to any one of the polynucleotides specified in (a)-(j), and that has a length that is at least 25% of the length of SEQ ID NO:7.

17. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 268;

(c) a fragment of the amino acid sequence of SEQ ID NO:8, the fragment comprising eight contiguous amino acids of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone ij1442_1 deposited under accession number ATCC 98755;

the protein being substantially free from other mammalian proteins.

18. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 335 to nucleotide 895;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 806 to nucleotide 895;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone pe213_1 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10, the fragment comprising eight contiguous amino acids of SEQ ID NO:10;

(j) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i); and

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i), and that has a length that is at least 25% of the length of SEQ ID NO:9.

19. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) a fragment of the amino acid sequence of SEQ ID NO:10, the fragment comprising eight contiguous amino acids of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe213_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

20. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 305 to nucleotide 928;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 641 to nucleotide 928;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone pe318_4 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12, the fragment comprising eight contiguous amino acids of SEQ ID NO:12;

(j) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i); and

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i), and that has a length that is at least 25% of the length of SEQ ID NO:11.

21. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) a fragment of the amino acid sequence of SEQ ID NO:12, the fragment comprising eight contiguous amino acids of SEQ ID NO:12; and

(c) the amino acid sequence encoded by the cDNA insert of clone pe318_4 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

22. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 640 to nucleotide 792;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pp85_1 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(f) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14, the fragment comprising eight contiguous amino acids of SEQ ID NO:14;

(g) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f); and

(h) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f), and that has a length that is at least 25% of the length of SEQ ID NO:13.

23. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) a fragment of the amino acid sequence of SEQ ID NO:14, the fragment comprising eight contiguous amino acids of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone pp85_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

24. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 641 to nucleotide 931;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone pp325_9 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(f) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16, the fragment comprising eight contiguous amino acids of SEQ ID NO:16;

(g) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f); and

(h) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f), and that has a length that is at least 25% of the length of SEQ ID NO:15.

25. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) a fragment of the amino acid sequence of SEQ ID NO:16, the fragment comprising eight contiguous amino acids of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone pp325_9 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

26. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 69 to nucleotide 443;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone qb401_6 deposited under accession number ATCC 98689;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(f) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18, the fragment comprising eight contiguous amino acids of SEQ ID NO:18;

(g) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f); and

(h) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(f), and that has a length that is at least 25% of the length of SEQ ID NO:17.

27. A protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) a fragment of the amino acid sequence of SEQ ID NO:18, the fragment comprising eight contiguous amino acids of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone qb401_6 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

28. An isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 151 to nucleotide 381;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 226 to nucleotide 381;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone qc671_1 deposited under accession number ATCC 98689;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20, the fragment comprising eight contiguous amino acids of SEQ ID NO:20;

(j) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 65 degrees C, or 4X SSC at 42 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i); and

(k) a polynucleotide that hybridizes under conditions at least as stringent as 4X SSC at 50 degrees C, or 6X SSC at 40 degrees C with 50% formamide, to any one of the polynucleotides specified in (a)-(i), and that has a length that is at least 25% of the length of SEQ ID NO:19.

29. A protein comprising an amino acid sequence selected from the group consisting of:

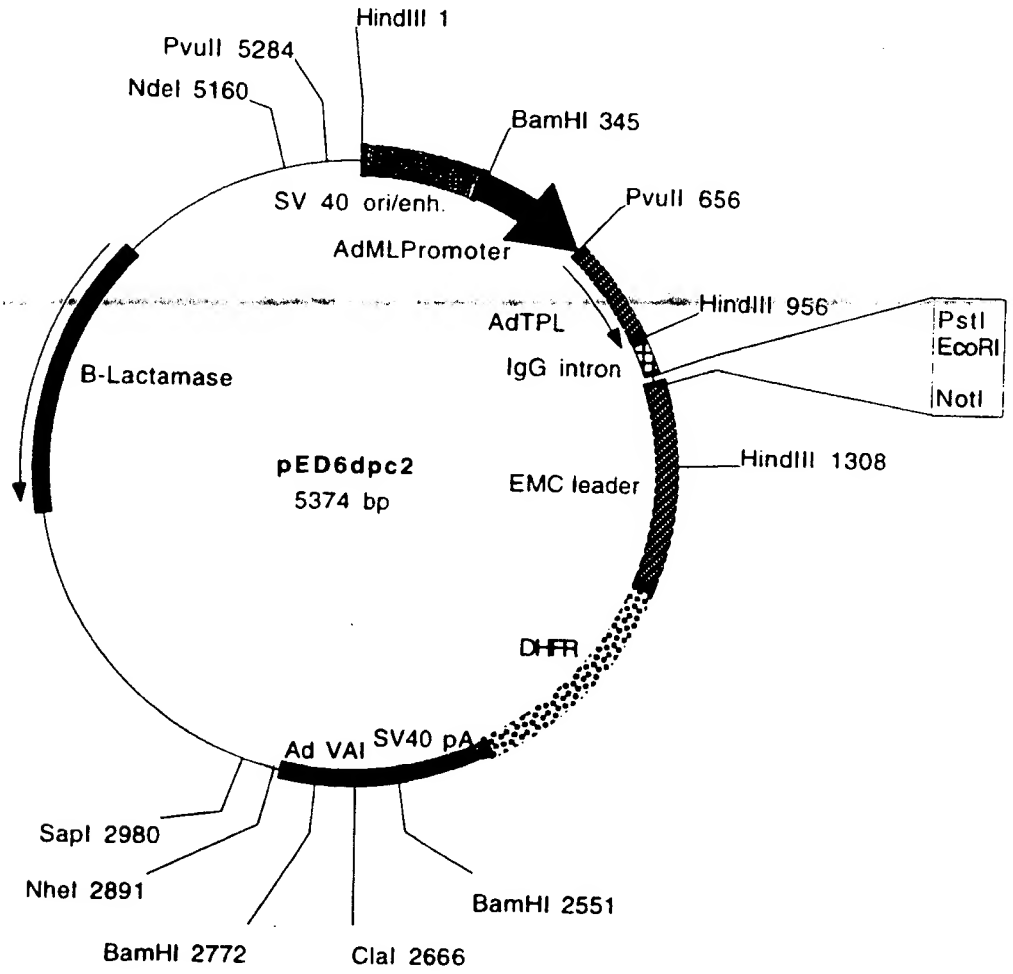
(a) the amino acid sequence of SEQ ID NO:20;

(b) a fragment of the amino acid sequence of SEQ ID NO:20, the fragment comprising eight contiguous amino acids of SEQ ID NO:20; and

(c) the amino acid sequence encoded by the cDNA insert of clone qc671_1 deposited under accession number ATCC 98689;

the protein being substantially free from other mammalian proteins.

FIGURE 1A



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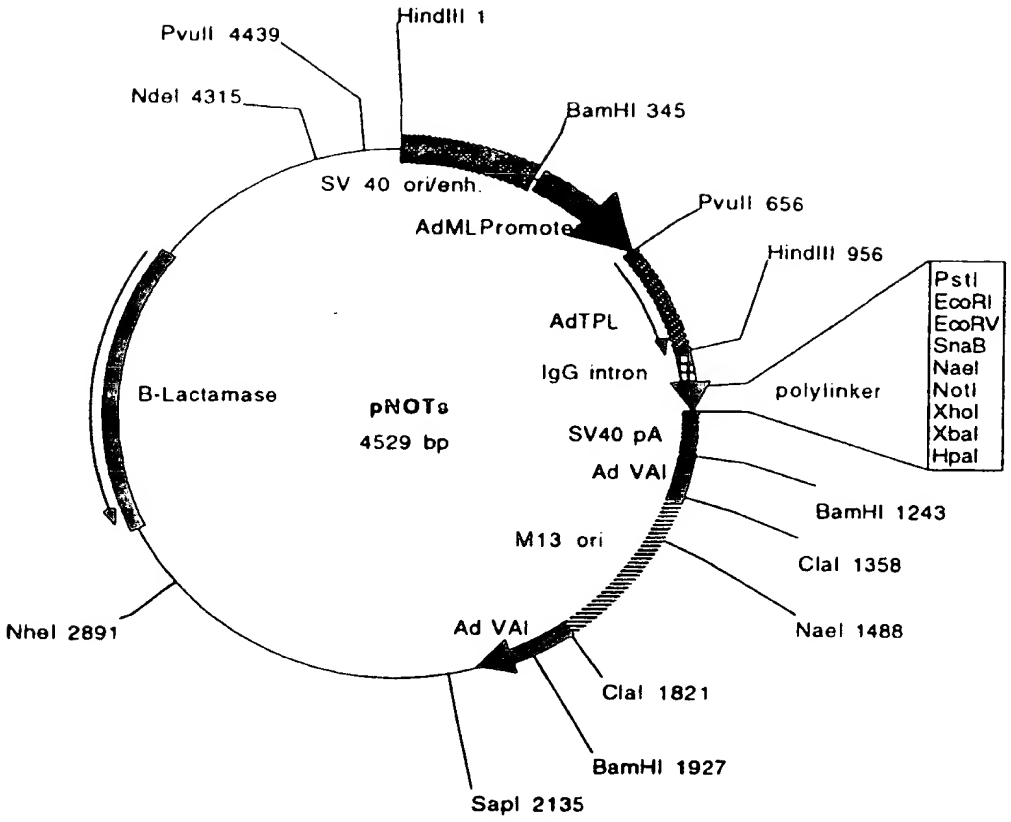
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI

SEQUENCE LISTING

<110> Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Collins-Racie, Lisa A.
Evans, Cheryl
Merberg, David
Treacy, Maurice
Agostino, Michael J.
Steininger II, Robert J.
Genetics Institute, Inc.

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<210> 6
<211> 99
<212> PRT
<213> Homo sapiens

<400> 6
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Phe Leu His Thr Ser Arg Thr Phe Val Leu Pro Val His Ala Val Lys
20 25 30

Asp Ser Ala Gln Val Leu Glu Glu Ile Val Lys His Glu Leu Gly Ser
35 40 45

Gln Val Ser Leu Leu Ser Pro Val Glu Glu Pro Gly Pro Ser Pro Cys
50 55 60

Thr Pro Asp Ile Gln Gly Arg Gly Val Arg Lys Thr Leu Pro Pro Asn
65 70 75 80

Gly Leu Asp Gly Met Phe Pro Ser Ser Cys Ser Pro Asn Val Ser Thr
85 90 95

Gly Ala His

<210> 7
<211> 1121
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> (1035)

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<210> 8
<211> 299
<212> PRT
<213> Homo sapiens

<400> 8

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Arg Ala Pro Arg Pro Pro Asp Gly Arg Gly Arg Val Arg Pro Arg Thr
            20                  25                  30

Gln Asp Gly Val Gly Asn His Thr Met Ala Arg Ile Pro Lys Thr Leu
        35                  40                  45

Lys Phe Val Val Val Ile Val Ala Val Leu Leu Pro Val Leu Ala Tyr
    50                  55                  60

Ser Ala Thr Thr Ala Arg Gln Glu Glu Val Pro Gln Gln Thr Val Ala
65                  70                  75                  80

Pro Gln Gln Gln Arg His Ser Phe Lys Gly Glu Glu Cys Pro Ala Gly
                85                  90                  95

Ser His Arg Ser Glu His Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly
            100                 105                 110

Val Asp Tyr Thr Asn Ala Ser Asn Asn Glu Pro Ser Cys Phe Pro Cys
        115                 120                 125

Thr Val Cys Lys Ser Asp Gln Lys His Lys Ser Ser Cys Thr Met Thr
    130                 135                 140

Arg Asp Thr Val Cys Gln Cys Lys Glu Gly Thr Phe Arg Asn Glu Asn
145                 150                 155                 160

Ser Pro Glu Met Cys Arg Lys Cys Ser Arg Cys Pro Ser Gly Glu Val
                165                 170                 175

Gln Val Ser Asn Cys Thr Ser Trp Asp Asp Ile Gln Cys Val Glu Glu
            180                 185                 190

Phe Gly Ala Asn Ala Thr Val Glu Thr Pro Ala Ala Glu Glu Thr Met
        195                 200                 205

Asn Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Asn
    210                 215                 220

Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr
225                 230                 235                 240

Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr Ser
                245                 250                 255

Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr Ser Pro
            260                 265                 270

Gly Thr Pro Ala Ser Ser His Tyr Leu Ser Cys Thr Ile Val Gly Ile
        275                 280                 285

Ile Val Leu Ile Val Leu Leu Ile Val Phe Val
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<210> 9
<211> 1005

<212> DNA
<213> Homo sapiens

<400> 9
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ttaccacctg gaatggttca tcaggggaaa ggacccccag cccgtggagg aggaaaagag 180
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tcctgctacc atgttgacag agccccagaa cccacatcta attggctttg ttgcttattc 420
tggcccttcc cacaccacac agccacacaa atactggctg ctccttgatg gccaggcaga 480
cccagcagca gccgaggggc cagtgaagag gaaggccgca tctgttgtgt ggtggccaca 540
agcactcagg catctgagtt tactggtgca ctgctgggag gagagttatg agatgaacat 600
tggctgtcaa tctctgtggg caggcggttt ggcctctagt gggaatggct gggatttggg 660
cgttgccttt aggagggata cctgcatgtc tagttccagt ctgcactgga aagaattcaa 720
atatgcacct ggctcccttc actattttgc cctatccttt gtgctcattc ttactgaaat 780
ctgtcttgtc agctcaggaa tgggattccc ccaggaagga aagcactttt ctgttctggg 840
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gagaaccata aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 1005

<210> 10
<211> 187
<212> PRT
<213> Homo sapiens

<400> 10
Met Val Leu Leu Trp Val Val Thr Cys Pro Ala Thr Met Leu Thr Glu
1 5 10 15

Pro Gln Asn Pro His Leu Ile Gly Phe Val Ala Tyr Ser Gly Pro Ser
20 25 30

His Thr Thr Gln Pro His Lys Tyr Trp Leu Leu Leu Asp Gly Gln Ala
35 40 45

Asp Pro Ala Ala Ala Glu Gly Pro Val Lys Arg Lys Ala Ala Ser Val
50 55 60

Val Trp Trp Pro Gln Ala Leu Arg His Leu Ser Leu Leu Val His Cys
65 70 75 80

Trp Glu Glu Ser Tyr Glu Met Asn Ile Gly Cys Gln Ser Leu Trp Ala
85 90 95

Gly Gly Leu Ala Ser Ser Gly Asn Gly Trp Asp Leu Gly Val Ala Phe
100 105 110

Arg Arg Asp Thr Cys Met Ser Ser Ser Ser Leu His Trp Lys Glu Phe
115 120 125

Lys Tyr Ala Pro Gly Ser Leu His Tyr Phe Ala Leu Ser Phe Val Leu
130 135 140

Ile Leu Thr Glu Ile Cys Leu Val Ser Ser Gly Met Gly Phe Pro Gln
145 150 155 160

Glu Gly Lys His Phe Ser Val Leu Gly Ser Pro Asp Cys Ser Leu Trp
165 170 175

Gly Arg Asp Glu His Val Pro Arg Glu Phe Ala
180 185

<210> 11
<211> 1198
<212> DNA
<213> Homo sapiens

<400> 11
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ctgttagaaa tgtggtggtt tcagcaaggc ctcagtttcc ttccttcagc ccttgtaatt 180
tggacatctg ctgctttcat attttcatac attactgcag taacactcca ccatatagac 240
ccggctttac cttatatcag tgacactggt acagtagctc cagaaaaatg cttattttgg 300
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agttcatgct ctgagtcctg aagagaacgt tatcatcaaa ttaaacaagg ctggccttgt 420
acttggaata ctgagttgtt taggactttc tattgtggca aacttccaga aaacaagcct 480
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gatcagactg ttgttggtta tctggtgtgg agtaagtgca cttagcatgc tgacttgctc 660
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gaagccattt gatagattat tctaaaggat atcatcaaga agactattaa aaacacctat 1140
gcctatactt ttttatctca gaaaataaag tcaaaagact atgaaaaaaa aaaaaaaa 1198

<210> 12
<211> 208
<212> PRT
<213> Homo sapiens

<400> 12
Met Leu Asn Ile Ala Ala Val Leu Cys Ile Ala Thr Ile Tyr Val Arg
1 5 10 15

Tyr Lys Gln Val His Ala Leu Ser Pro Glu Glu Asn Val Ile Ile Lys
20 25 30

Leu Asn Lys Ala Gly Leu Val Leu Gly Ile Leu Ser Cys Leu Gly Leu
35 40 45

Ser Ile Val Ala Asn Phe Gln Lys Thr Thr Leu Phe Ala Ala His Val
50 55 60

Ser Gly Ala Val Leu Thr Phe Gly Met Gly Ser Leu Tyr Met Phe Val
65 70 75 80

Gln Thr Ile Leu Ser Tyr Gln Met Gln Pro Lys Ile His Gly Lys Gln
85 90 95

Val Phe Trp Ile Arg Leu Leu Leu Val Ile Trp Cys Gly Val Ser Ala
100 105 110

Leu Ser Met Leu Thr Cys Ser Ser Val Leu His Ser Gly Asn Phe Gly

```
        115                 120                 125

Thr Asp Leu Glu Gln Lys Leu His Trp Asn Pro Glu Asp Lys Gly Tyr
    130                 135                 140

Val Leu His Met Ile Thr Thr Ala Ala Glu Trp Ser Met Ser Phe Ser
145                 150                 155                 160

Phe Phe Gly Phe Phe Leu Thr Tyr Ile Arg Asp Phe Gln Lys Ile Ser
                165                 170                 175

Leu Arg Val Glu Ala Asn Leu His Gly Leu Thr Leu Tyr Asp Thr Ala
            180                 185                 190

Pro Cys Pro Ile Asn Asn Glu Arg Thr Arg Leu Leu Ser Arg Asp Ile
        195                 200                 205
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<210> 13
<211> 1164
<212> DNA
<213> Homo sapiens

<400> 13

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atgtgctttc tgggtgacag caagactcta tctaaaaaca gagaaagaaa cccagacgag 180
cataagccca gtgtagacag aattgtgatg gagtgtattt catgtagcac cactggcctc 240
atgttcaaag gctttcatgt gccaagggcg ctggacccac tcccagggtg caccactgac 300
tcaccaccca gtgaaataat tgctgggttc aaaggcatag agttggaaaa gtgtcgattg 360
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ctgggtaaag gacaatggtc cacatccgtg ggtggcatga ctggagagct gtgggaagaa 480
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ctccatctca aaaaaaaaaa aaaa                                        1164
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<210> 14
<211> 51
<212> PRT
<213> Homo sapiens

<400> 14

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Met Val Lys Ala Cys Thr Cys Phe Arg Phe Leu Asn Met Thr Ser Leu
  1               5                  10                  15

Phe Pro Val Leu Trp Tyr Ile His Ala Ile Pro Ser Ala Trp Asn Ile
            20                  25                  30

Ser Pro His Pro Gln His Gln Glu Lys Leu Arg Ala Lys Ser Leu Val
        35                  40                  45
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Arg Gln Ser
50

<210> 15
<211> 1938
<212> DNA
<213> Homo sapiens

<400> 15
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acttttctcc catcttattt atttttctgt agatattttg attcattata aaacatctat 180
ttttaaaagt cagatttcag ctttgtaaaa tgaaaaatat accatcagta ttgaacaaaa 240
tattagttga atctcttctt ctggaatgtc ccaatagctt tttgtggtta ctcatcgtgg 300
aaggttgtaa tgccctagca ttacagattt tagggatgct aactgctggt gttgaagaat 360
aactgctgta ggaaaaaaaa ttagtgtaat tttaataaca ttgactatta gcatttaaca 420
cagaactatt ttcatcatca acaagtttat tcagctcatt ctaaatggtc ccttatataa 480
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cgcaaaaaaa aaaaaaaa 1938

<210> 16
<211> 97
<212> PRT
<213> Homo sapiens

<400> 16
Met Asn Tyr Tyr Gln Met Leu Ile Ile Tyr Tyr Val Leu Phe Phe Lys
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Val Asn Glu Phe Leu Ala Phe Glu Gly Pro Ile Leu Leu Asp Met Arg
20 25 30

Ile Lys His Leu Ile Lys Thr Asn Gln Leu Ser Gln Ala Thr Ala Leu
35 40 45

Ala Lys Leu Cys Ser Asp His Pro Glu Ile Gly Ile Lys Gly Ser Phe

50 55 60

Lys Gln Thr Tyr Leu Val Cys Leu Cys Thr Ser Ser Pro Asn Gly Lys
65 70 75 80

Leu Ile Glu Glu Val Ser Met Phe Ser Phe Ile Ser Asn Tyr Phe Phe
85 90 95

Ser

<210> 17
<211> 2185
<212> DNA
<213> Homo sapiens

<400> 17
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gcaccagtgc actctagcct gggtcacaga gcaagactct gcctcaaaaa caaaaacaaa 720
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<210> 18
<211> 125
<212> PRT
<213> Homo sapiens

<400> 18
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Leu Pro Gln Phe Gln Gly Ala Tyr Ser Lys Val Leu Pro Asn Cys Gly
20 25 30

Leu Gln Gly Pro Ala Trp Ser Thr Phe Ala Arg Leu Phe Asn Leu Thr
35 40 45

Ser Thr Thr Phe Pro Leu Ser His Ser Pro Gln Pro Leu Arg Ser Ser
50 55 60

Phe Thr Cys Gly Asp Met Pro Ser Val Cys Cys Leu Arg Thr Phe Ala
65 70 75 80

His Val Phe Pro Leu Leu Gly Met Leu Ser Leu Pro Ser Phe Pro Thr
85 90 95

Phe Phe His Ala Ser Pro Phe His Pro Leu Gly Val Cys Ile Cys Gly
100 105 110

Pro Phe Ser Trp Gln Leu Phe Leu Ala Ser Leu Trp Lys
115 120 125

<210> 19
<211> 987
<212> DNA
<213> Homo sapiens

<400> 19
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acccagtgac actctcaagg tgctgacaaa atggacatgg acatttgttg cttttcttct 180
tttgaattag gaactctatt gtgtttcctg aatttactgt ctgcttggcc catgatcctg 240
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ggtagaagct actactctca atgccattct aaaattgacg aagagtatta ttttccccaa 360
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Thr Ile Leu Pro Tyr Pro Leu Cys Ser Phe Leu Leu Lys Ser Val Leu
        35                  40                  45

Ser Ala Gln Glu Trp Asp Ser Pro Arg Lys Glu Ser Thr Phe Leu Phe
    50                  55                  60

Trp Glu Ala Gln Thr Val His Phe Gly Ala Gly Thr Asn Met Cys Leu
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Arg Ala Leu Asp Pro Leu Pro Gly Cys Thr Thr Asp Ser Pro Pro Ser
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His Gly Ser Phe Ser Trp Pro Ala Tyr Gly Ser Arg Ser Ile Arg His
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Pro Ser Leu Glu Phe Val Phe Ser Ile Glu His Leu Pro Val Tyr Asn
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05243

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 14/147, 14/00, 7/00; C12N 5/10, 15/10, 15/11, 15/12, 15/63

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300, 350; 536/23.1, 23/5; 435/69.1, 320.1, 325, 252.3, 254.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

GenBank, WPIDS, APS
search terms: kenneth jacobs, cb98?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIALLINAS et al. Genetic and molecular characterization of a gene encoding a wide specificity purine permease of *Aspergillus nidulans* reveals a novel family of transporters conserved in prokayrotes and eukaryotes. J. Biol. Chem. 14 April 1995. Vol. 270, No. 15, pages 8610-8622, especially Figures 5 and 7.	1-3, 5-7, 9, 11
X	HILLIER et al. GenBank Database, National Library of Medicine, Bethesda, Maryland USA, Accession Number W31918, zc76h07.sl Pancreatic islet Homo sapiens cDNA clone 328285 3', 10 May 1996, see entire document.	1-3

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
27 MAY 1999	08 JUL 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CLAIRE M. KAUFMAN Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NCI-CGAP, GenBank Database, National Library of Medicine, Bethesda, Maryland USA, Accession No. AA811390, ob82d11.sl NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:1337877 similar to TR:Q14221 Q14221 ENDOSOME-ASSOCIATED PROTEIN, 19 FEBRUARY 1998, see entire document.	1-3
A	JACOBS et al. A genetic selection for isolating cDNA encoding secreted proteins. Gene. January 1997, Vol. 198, pages 289-296.	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05243

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05243

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

530/300, 350; 536/23.1, 23.5; 435/69.1, 320.1, 325, 252.3, 254.11

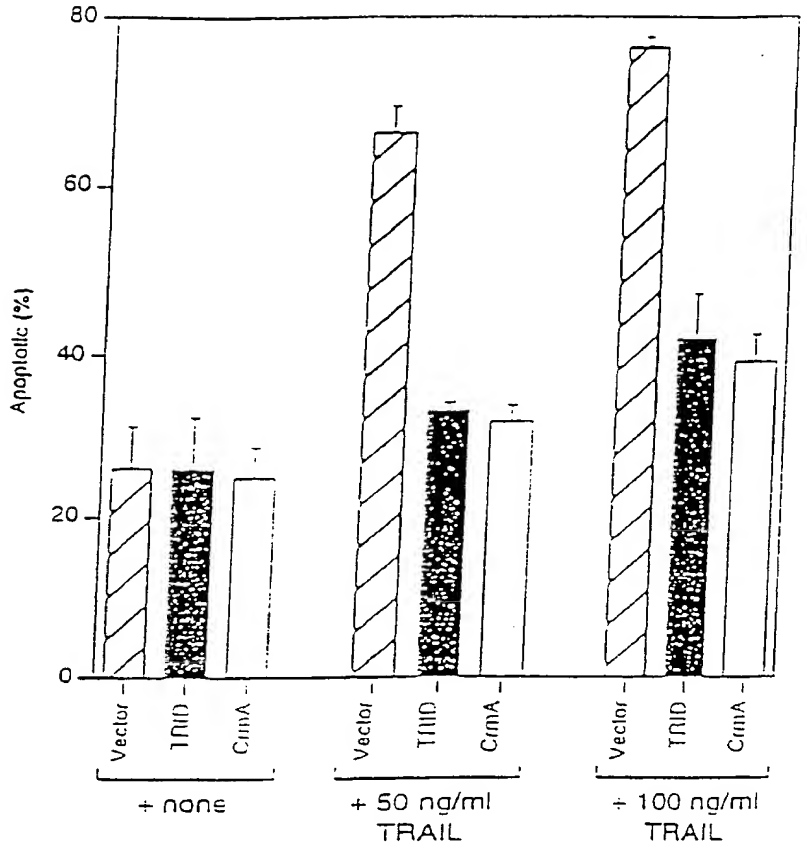
BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-11, drawn to polynucleotide of clone cb98_4, polynucleotide linked to an expression control sequence, host cell, method of producing a protein, encoded protein and composition comprising the protein.
Group II, claim(s) 12-13, drawn to polynucleotide of clone du515_21 and encoded protein.
Group III, claim(s) 14-15, drawn to polynucleotide of clone gn82_6 and encoded protein.
Group IV, claim(s) 16-17, drawn to polynucleotide of clone ij1442_1 and encoded protein.
Group V, claim(s) 18-19, drawn to polynucleotide of clone pe213_1 and encoded protein.
Group VI, claim(s) 20-21, drawn to polynucleotide of clone pe318_4 and encoded protein.
Group VII, claim(s) 22-23, drawn to polynucleotide of clone pp85_1 and encoded protein.
Group VIII, claim(s) 24-25, drawn to polynucleotide of clone pp325_9 and encoded protein.
Group IX, claim(s) 26-27, drawn to polynucleotide of clone qb401_6 and encoded protein.
Group X, claim(s) 28-29, drawn to polynucleotide of clone qc671_1 and encoded protein.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I corresponds to the first invention wherein the first product is the polynucleotide and the first method of using is the method of making the protein. The invention also includes the protein made. Each group does not share the same or corresponding special technical feature because each group is drawn to a different polynucleotide and encoded protein. This Authority therefore considers that the several inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1

FIGURE 6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60
40
20
0
Apoptotic (%)
Vector
TNID
CrmA
+ none
+ 50 ng/ml TRAIL
+ 100 ng/ml TRAIL